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FAX: 201-524-9711
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October 14, 1999

Documents Management Branch
HFD-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Ref: Docket No. 99D-2636

Re: Comments provided to Draft Guidance for Industry on Levothyroxine Sodium

Dear Sir or Madam:

Forest Laboratories, Inc. wishes to provide comments to the above referenced Draft Guidance. Please find attached two copies.

Respectfully submitted,

FOREST LABORATORIES, INC.

Gilbert W. Adelstein, Ph.D.
Director of Regulatory Affairs

99D-2636

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II. REGULATORY QUESTIONS AND ANSWERS

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A. Status of Marketed Products

Q: After August 14, 1997, is it permissible to begin marketing an unapproved levothyroxine sodium product that has never before been marketed?

A: No. As stated in the *Federal Register* notice, any levothyroxine sodium product marketed *for the first time* after August 14, 1997, must have an approved new drug application. Any product marketed without an approved application is an unapproved new drug and subject to enforcement action.

Q: On August 14, 2000, what will be the status of a marketed product if an application for that product was submitted prior to August 14, 2000, but is not yet approved as of that date?

A: *Any* levothyroxine sodium product marketed on or after August 14, 2000, without an approved NDA will continue to be considered an unapproved new drug and will be subject to enforcement action (62 FR 43535, August 14, 1997). This will be the case even if an application for the product is undergoing review. Whether FDA will initiate enforcement action to remove an unapproved product from the market will depend upon its enforcement priorities and resources.

Comment:

Until July 27, 1999 the agency did not address the standards to be applied in the design and conduct of CMC stability studies for L-thyroxine. On that date, almost 2 years after the August 14, 1997 *Federal Register* Notice it issued a six paragraph statement, without prior notice or providing an opportunity for comment, that significantly restricted, without explanation, previously utilized stability study practices which had not been considered to be outside of cGMP. The July 27 statement did not explain why FDA considered its specifications as essential to be followed. In any event, it is clear that the one-year time period between July 27, 1999 and August 14, 2000, is insufficient to allow data generation and compilation which would be adequate to support an expiration date with a minimum of 24 months of a newly formulated product. It is critical that the August 14, 2000 date be extended to August 14, 2002.

B. Cutoff Date for 505(b)(2) Applications

Q: Will FDA approve only one NDA and convert other 505(b)(2) applications to ANDAs?

A: No. It is possible that more than one NDA will be approved. FDA will not convert any filed NDA to an ANDA.

Q: Will there be a cutoff date after which FDA will no longer accept and review 505(b)(2) applications?

A. FDA will review all 505(b)(2) applications for levothyroxine sodium products filed before the first NDA for levothyroxine sodium products is approved. After the first NDA for levothyroxine sodium is approved, FDA may refuse to file any 505(b)(2) application for a drug product that is a duplicate of the product approved in the first NDA. If an application is refused for filing, it may be resubmitted as an ANDA, provided it meets the requirements of section 505(j) of the Act.

Comment:

As stated above, the August 14, 2000 filing date does not provide sufficient time for reformulation of an old product, if required, generation of stability and bioequivalence data, and submission of the NDA. This date should be extended to August 14, 2002.

Q: What will happen to a 505(b)(2) application that has been filed, but not yet approved, when the first NDA for levothyroxine sodium is approved? What if the application was submitted, but not filed, when the first NDA is approved?

A: FDA will review all NDAs, including 505(b)(2) applications for duplicates, that have been filed even if an NDA is approved before review of an application has been completed. The FDA may refuse to file and review a 505(b)(2) application that was submitted, but not filed, before the first NDA for levothyroxine sodium is approved.

C. Requirements for 505(b)(2) Applications

Q: Should a 505(b)(2) application contain a patent certification?

A: All 505(b)(2) applications are subject to the patent certification requirements at 21CFR 314.50(i). However, if there is no listed drug for levothyroxine sodium at the time the application is filed, the applicant need not make a patent certification.

After an NDA is approved and there is a listed drug, applications that have been submitted or filed, but not yet approved, must be amended to contain a patent certification for each patent listed for the approved product (21 CFR 314.50(i)). If there are no patents listed for the approved product, the applicant should submit a statement, as described at 314.50(i)(1)(ii), that there are no relevant patents.

Q: Will a 505(b)(2) application for levothyroxine sodium be assessed a user fee? If so, is it a full fee or half fee?

A: Yes, a user fee will be assessed. The Act provides that a 505(b)(2) application is subject to an application fee if it requests approval of either (1) a molecular entity that is an active ingredient (including any salt or ester of an active ingredient) that has not been approved under section 505(b) of the Act, or (2) an indication for a use that has not been approved under section 505(b) of the Act (sections 735(1)(B) and 736(a)(1)(A)(i) of the Act). Levothyroxine sodium has been approved previously as an active ingredient in two NDAs (NDA 16-807, Thyrolar, and NDA 16-680, Euthroid). However, levothyroxine sodium as a single-agent therapy has not been approved for any indication. Therefore, the FDA believes that single-agent therapy for thyroid-related disorders is a new indication for use. Therefore, applicants submitting 505(b)(2) applications for levothyroxine sodium must pay a user fee. But once an application has been approved, another 505(b)(2) application for levothyroxine sodium would not be subject to a fee unless the applicant seeks approval of an indication different from that approved in earlier applications. A full fee would be assessed because clinical data (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are required for approval (section 736(a)(1)(A)(i) of the Act). These clinical data are expected to be in the form of literature reports, but are still considered to be clinical data for purposes of assessing user fees.

An applicant submitting a 505(b)(2) application for levothyroxine sodium may be eligible for a waiver or reduction of user fees under section 736(d) of the Act. For information on how to apply for a waiver, you may contact the Regulatory Policy Staff, CDER, HFD-7, 5600 Fishers Lane, Rockville, Maryland 20857, 301-594-2041.

Comment:

Section 505(b)(2) applications for levothyroxine sodium for the treatment of hypothyroidism, as called for in the *Federal Register* of August 14, 1997 are, by statute, not subject to user fees. Prior to adoption of the "human drug application" definition in the Prescription Drug User Fee Act of 1992 (in which the definition is the same as in FDAMA) the question of the status of § 505(b)(2) applications under that definition was addressed on the House Floor in the "Statement of Floor

Manager Explaining Changes Made After Committee Consideration of HR 5952," (page H9099, Sept. 22, 1992). A copy of the most directly pertinent paragraph is set out below:

> The change, made after the bill was reported by the committee but which is in the bill, would limit the § 505(b)(2) applications included within the definition of "human drug application" – § 735(1)(B), as added by section 3 – to applications that request approval of first, [a] molecular entity which is an active ingredient or second, an indication for a use that had not been approved under § 505(b). The Committee intends that the term "indication" be given the meaning that it is given in the FDA's regulations, 21 C.F.R. § 201.57(c), 1992. This term would include an Rx to OTC switch. User fees would not be required for any other new drug approved under § 505(b)(2).

The context of FDA's regulation at 21 C.F.R. § 201.57(c)(1)(i) through (iv) reveals that no substantive distinction was drawn between "indication" as used in the cited regulation and "indication for a use" as used in § 735(1)(B)(ii). If "an active ingredient" had been approved in a §505(b) application before September 1, 1992, with "an indication for use" of that ingredient , a §505(b)(2) applicant for a drug product containing that same ingredient and the previously approved indication for use would not come within the definition of "human drug application" and therefore would not be subject to a user fee. This User Fee exclusion provision clearly applies to §505(b)(2) applications addressed to the use of levothyroxine sodium in the treatment of hypothyroidism. The "indication" in this situation is the "treatment of hypothyroidism," and the active ingredient is levothyroxine sodium. Both the indication and the ingredient have been previously approved for Thyrolar and Euthroid. "Single-agent" therapy is not a statutory element or a practical requirement since the August 14, 1997 Notice recognizes the efficacy of levothyroxine as a single entity.

Q: Are pediatric studies necessary?

A: As of April 1, 1999, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration must contain a pediatric assessment, unless such studies are waived or deferred. Studies that are deferred are not required to be submitted until at least December 2, 2000.[3]

Applications for levothyroxine sodium are subject to the pediatric rule. Applicants should discuss with the division the need for a pediatric assessment for the levothyroxine product proposed in an NDA. It is possible that adequate data to support safety and effectiveness for pediatric use may be available in the scientific literature.

D. Exclusivity

Q: Will there be exclusivity for the first levothyroxine sodium product to be approved?

A: Exclusivity determinations are made at the time a drug product is approved. Although FDA cannot at this time be specific as to which, if any, applications may receive exclusivity, sponsors should consider some issues regarding the requirements for exclusivity. Five-year exclusivity is available for new chemical entities, which are drugs that contain no previously approved active moiety.

Levothyroxine sodium has previously been approved as an active ingredient in two NDAs (NDA 16-807, Thyrolar, and NDA 16-680, Euthroid). Three-year exclusivity is available for applications that contain reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant.

Comment:

If the determination is made by the FDA that clinical studies are essential to the approval of NDAs that meet the criteria of the August 14, 1997 Notice, each such NDA should be awarded an exclusivity period.

E. Therapeutic Equivalence Ratings for Levothyroxine Sodium Products

Q: If the Agency approves multiple 505(b)(2) applications, how will they be rated in the Orange Book?

A: They will be listed as BX **C** drug products for which the data are insufficient to determine therapeutic equivalence. To obtain a therapeutic equivalence rating other than BX for levothyroxine sodium tablets, an applicant must submit data comparing its product to a listed drug (*Approved Drug Products with Therapeutic Equivalence Evaluations* -- The Orange Book).

Q: Will FDA review a bioequivalence study submitted with an NDA that compares the product to an approved levothyroxine sodium product?

A: Yes. An NDA applicant may submit a bioequivalence study comparing its levothyroxine sodium product to one previously approved. If the products are bioequivalent, they will be AB-rated to each other.

F. ANDAs for Levothyroxine Sodium Products

Q: When will FDA choose a reference listed drug?

A: FDA chooses a reference listed drug when a manufacturer makes a request to submit an ANDA for a product that is eligible for approval under section 505(j) of the Act.

Q: How will FDA choose a reference listed drug for levothyroxine sodium tablets?

A: If there is only one approved product, that product will become the reference listed drug. If more than one product has been approved before FDA receives a request to submit an ANDA, the market leader among the approved products will be designated as the reference listed drug. FDA may also designate an additional reference listed drug if requested to do so by an ANDA sponsor.

Q: Will there be more than one reference listed drug?

A: It is possible.

Comments:

We believe that each currently marketed product should be given the opportunity to submit an NDA. FDA should review all studies submitted in the NDA including a bioequivalence study and approve the bioequivalence study, whether or not another levothyroxine product has been previously approved. Once the other product is approved, at that time an AB-rating for the two products should be granted and included in the Orange Book.

III. SCIENTIFIC QUESTIONS AND ANSWERS

A. Stability Data

Q: How much stability data is required for an application to be acceptable for filing?

A: ICH and FDA stability guidances recommend 12 months' long-term data and 6 months' accelerated data at the time of NDA submission if a 24-month expiration date is requested. However, for levothyroxine sodium products to meet the compliance date specified in the August 14, 1997, *Federal Register* notice, 6 months' long-term data and 3 months' accelerated data will be sufficient. Additional stability data may be submitted as an amendment during the review process, and an expiration date will be granted based on the data submitted.

Comment:

On July 27, 1999, the FDA Division of Metabolic and Endocrine Drug Products issued a document entitled "Guidelines for Submission of CMC Stability Studies For NDA for L-thyroxine." This was almost two years following the Federal Register notice of August 14, 1997. Previously, no official notice of ICH stability requirements had been issued. If the sponsor of a NDA began stability studies under ICH conditions on July 27, 1999, and successfully collected the 3 months' accelerated and 6 months' long-term data, the NDA submission could not take place until well after January 27, 2000. Assuming an additional 6 months of stability data were to be submitted as an amendment to the pending NDA on July 27, 2000, the FDA would have to review and approve the NDA before August 14, 2000, barely 18 days following the latest amendment. This scenario can not realistically be accomplished and illustrates the need for an appropriate time extension for submission and approval of an application.

The imposition of ICH stability storage conditions was intended "only for new molecular entities and associated drug products" (ref: Draft Guidance for Industry; Stability Testing of Drug Substances and Drug Products, May 1998). Although FDA considers L-thyroxine products subject to new drug classification, they have been available and used in medical practice for years. While specified as a new molecular entity for purposes of the NDA, this product has existed in medical practice for years and recognized as essential in the August 14, 1999 Federal Register notice. Manufacturers may still be using adequate and appropriate formulations for products that were never meant to support stability storage temperatures and humidity levels required by contemporary standards. The authors of the Draft Guidance for Industry recognized this and stated that for products already approved, or in this case marketed, "applicants may wish to voluntarily switch to the ICH-recommended storage conditions as defined in ICH Q1A and Sections II.A.4. and II.B.5. of this guidance."

The instability of L-thyroxine formulations under conditions of moisture and heat is well-documented, as has been pointed out in the Federal Register Notice of August 14, 1997. Therefore, applying ICH stability requirements to a product with known sensitivities to ICH conditions will likely result in stability failures. For products that have not been reformulated, the stability storage conditions should remain unchanged from the pre-NDA condition.

Since levothyroxine sodium belongs to a class of products marketed prior to the promulgation of the ICH stability conditions, real time stability data from the marketed product should be sufficient. Stability data compiled from data of marketed lots stored under 25+/-2 degrees and

ambient humidity conditions should be accepted. Submission of accelerated storage data should be waived for this product due to the availability of real time data and the known detrimental effect of high temperature and humidity on the active ingredient.

FDA has recognized that "levothyroxine sodium is unstable in the presence of light, temperature, air, and humidity." [62 FR 43537]. As a consequence, manufacturing methods have been developed to compensate for such circumstances. These include manufacturing a batch in conformity with the standards of cGMPs with a fixed overage of active ingredient. For a defined period after manufacture, the batch is "aged" for a specified time. During the aging period a reduction in the level of active ingredient takes place which will decelerate after the passage of a known time period. At the time of release, the batch will be within USP specifications and remain so throughout its expiry period. Whether the described practice involves a "stability overage" or a "manufacturing overage" is a question of semantics. So long as it can be shown that all of the manufacturing practices followed are defined and validated and the product remains within specification throughout the period from its release to expiration, the described course of manufacture should be recognized as acceptable.

As stated above, it has been established that levothyroxine sodium drug substance is unstable in the presence of light, temperature, air and humidity. The fact that a formulation and/or packaging configuration may or may not compromise stability in response to extreme environmental factors does not necessarily relate to the long-term stability of these products. A compilation of all relevant historical stability data for levothyroxine sodium products should suffice to show that the packaging and storage requirements of these products and their expiration dating have been suitably established. Moreover, re-examination of the stability of these products under the ICH accelerated or controlled-room temperature has no relevance to concerns raised regarding the inadequacy of stability test procedures or of the ability to prevent occasional instances of superpotency.

B. Dissolution Test

Q: The USP proposed a new dissolution test for levothyroxine sodium in the January-February 1999 *Pharmacopeial Forum*. Should NDA applicants use that proposed test or continue to use the current official method?

A: The proposed new dissolution test has not been adopted. Applicants should use the current official USP test. If the USP changes the official test after an NDA is submitted, an applicant can submit new data using that test as a phase-4 study.

Comment:

According to the guidance "*In Vivo* Pharmacokinetics and Bioavailability Studies and *In Vitro* Dissolution Testing for Levothyroxine Sodium Tablets", dissolution studies can be performed using the current USP method or others provided that justification for the choice of the method is given. Therefore, the applicant's procedure, if different from the current compendium method, should also be considered acceptable when given with the appropriate justification.

C. Overage

Q: May a stability overage be used?

A: No.

Comment:

A stability overage may be required for selected products. A more valid concern raised by FDA relates to the issue of sub- or super- potency. Based on FDA's own research, a stability overage is necessary otherwise subpotent products will result. If the manufacturer can show that there are no instances of superpotency in products released to the marketplace, then the formulation manufactured with stability overages should be allowed. The dosage should be formulated with the intent to provide 100 percent of the quantity of the active ingredient declared. Where historical data establishing the content of the active to decrease with time, an amount in excess of the declared on the label may be introduced into the dosage form at the time of manufacture to assure compliance with the content requirements of the label throughout the expiration period. This will assure that a super-potent product will not be released to the marketplace. Thus stability overage should be allowed when justified and where the product meets compendial requirements for content uniformity and potency at the time of release.

Q: May a manufacturing overage be used?

A. Yes. The FDA permits the use of a manufacturing overage only in the unusual case when the product is manufactured to be 100 percent potent at the time of release and when the manufacturer can specifically document where in the manufacturing process the loss of potency occurs.

Comment:

A manufacturing overage is sometimes required. There should be no need to specifically document where in the manufacturing process a loss of potency occurs. The fact that a loss occurs combined with product release data demonstrating that the product is neither subpotent nor superpotent should suffice. The FDA and USP both permit the use of a manufacturing overage where there is data supporting potency loss during the manufacturing process.

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